



PATENT
Customer No. 22,852
Attorney Docket No. 05725.0213-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:)
Paolo GIACOMONI) Group Art Unit: 1615
Application No.: 08/894,788) Examiner: L. Channavajjala
Filed: February 9, 2000)
For: NITRIC OXIDE SYNTHASE) Confirmation No.: 9346
INHIBITORS)

Mail Stop Appeal Brief--Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REPLY BRIEF UNDER 37 C.F.R. § 1.193

Pursuant to 37 C.F.R. § 1.193, Appellant presents in triplicate a reply to the Examiner's Answer, dated May 4, 2004, and an accompanying Request for Oral Hearing. The due date of the Reply Brief having been extended to July 6, 2004 with July 4, 2004 Federal holiday being celebrated on July 5, 2004.

If any fees are required in connection with the filing of this paper that are not filed herewith, Appellant requests that the required fees be charged to Deposit Account No. 06-0916.

REMARKS

In response to Appellant's Brief filed July 30, 2003, the Examiner maintains her position that the presently claimed invention is *prima facie* obvious over U.S. Patent No. 5,716,625 to Hahn et al. ("Hahn") in view either of U.S. Patent No. 5,358,969 to Williamson et al. ("Williamson") or U.S. Patent No. 5,449,688 to Wahl et al. ("Wahl"), or both. See Examiner's Answer dated May 4, 2004. Appellant respectfully continues to disagree for the reason of record and the additional reasons presented below.

I. Response to Examiner's Answer

A. Teachings of the Primary Reference, Hahn

The Examiner continues to assert that "the motivation to replace the strontium of Hahn et al. with the nitric oxide synthase inhibitors of Williamson et al. comes from the fact that both references teach the treatment of [the] same skin conditions (dermatitis, chemical and environmental irritation etc.)." Examiner's Answer at page 5, line 21-page 6, line 3. Appellant, however, disagrees, as the Examiner's statement continues to disregard relevant teachings of the cited references, thereby distorting what would otherwise be "fairly suggested" to one of ordinary skill in the art. See *In re Burckel*, 592 F.2d 1175, 1179, 201 U.S.P.Q. 67, 70 (C.C.P.A. 1979) ("[A] reference must be considered not only for what it expressly teaches, but also what it fairly suggests.").

In fact, throughout the Examiner's Answer, there is a continued indifference shown for the express teachings of the cited references in hopes of creating Appellant's invention. "Our case law[, however,] makes clear that the best defense against the subtle but powerful attraction of a hindsight based obviousness analysis is rigorous

application of the requirement for a showing of the teaching or motivation to combine the prior art references." *In re Dembicza*k, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999).

In the Examiner's Answer, the Examiner states that "Williamson et al. teaches nitric oxide synthase inhibitors as a treatment for dermatitis, sunburn, etc., while Hahn teaches strontium chloride for the same." Examiner's Answer at page 6, II. 3-5. This is not so. In fact, to the contrary, Williamson is concerned with the treatment of the systemic condition itself, i.e., preventing inflammation (dermatitis), while Hahn is directed to the topical treatment of the symptoms of irritation associated with or caused by such a condition. As provided below, the respective reference teachings are distinctly different because one treats a systemic condition, while the other treats symptoms of that condition.

Hahn expressly states that "the present invention . . . is useful in reducing the incidence and severity of *irritation* associated with topically applied skin irritants." Hahn at Col. 4, line 65-Col. 5, line 1 (emphasis added). Further, the divalent strontium in Hahn may be used "to inhibit or modify the action of cell proteases or other irritation-inducing biological molecules . . ." Hahn at Col. 5, II. 21-26. As such, these statements clearly suggest that Hahn is directed toward treatment of a particular symptom, i.e., irritation, associated with or caused by topical application of irritants or biological molecules that are irritants.

Williamson, however, states that his invention "inhibit[s] nitric oxide formation in warm blooded mammals afflicted with acute or chronic inflammatory disease."

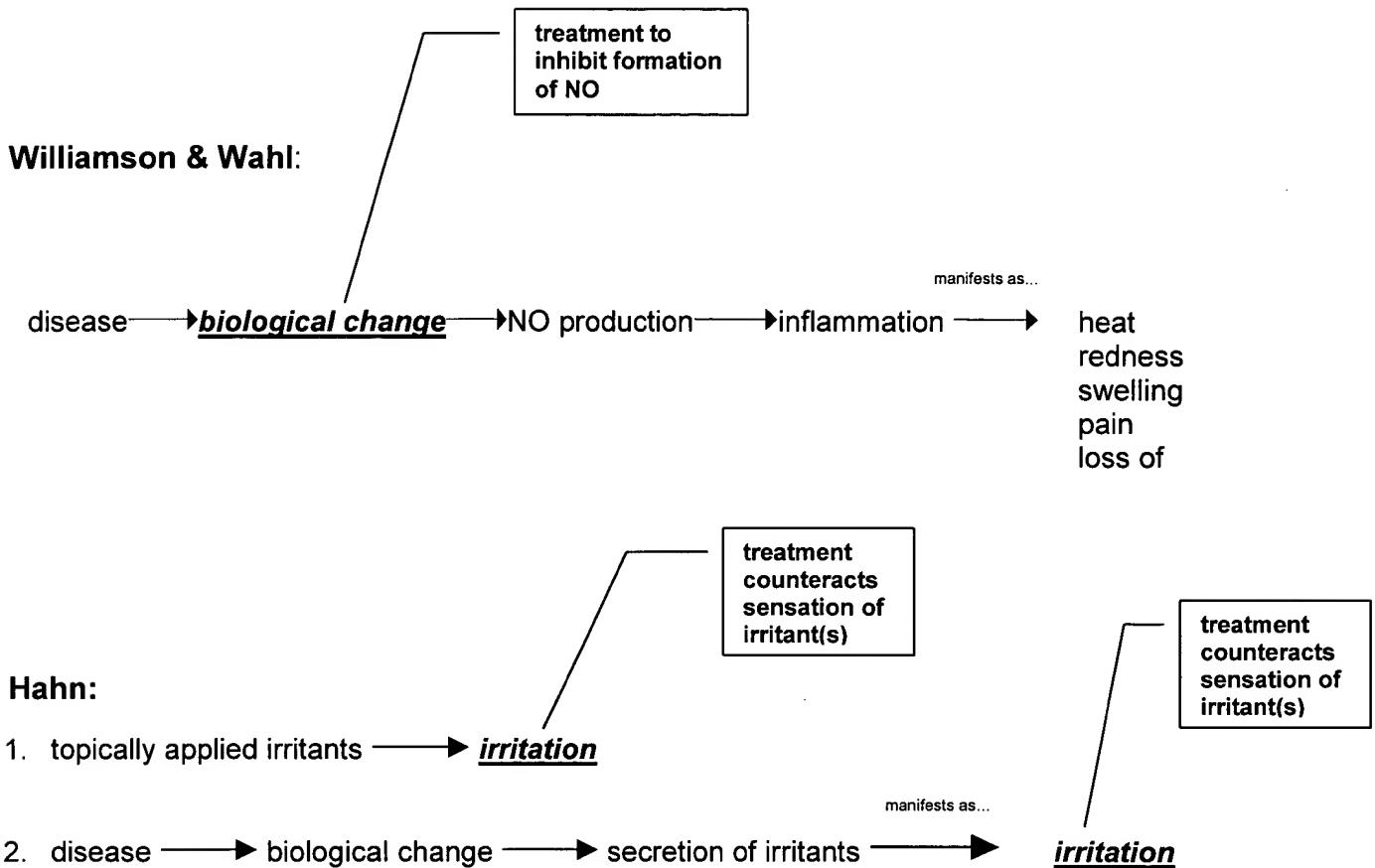
Williamson at Col. 2, ll. 44-47. Inflammation, as provided by Williamson, manifests as heat, redness, swelling, pain, and loss of function, not symptomatic irritation.

Williamson at Col. 3, ll. 1-2.

Although Hahn indicates there is a need for compounds that can combat topical as well as intrinsic irritation of the skin, this stated desire does not amount to the suggestion of application of Hahn's invention to reduce systemic inflammation. Nowhere does Hahn correlate reduced symptomatic irritation to a reduction of skin inflammation produced by an internal cause or reaction.

To the contrary, Hahn suggests and in fact, teaches that "agents which are effective to combat one source of sensory stimulus – for example steroidal agents to treat skin *inflammation* – are *ineffective* against other sensory stimuli such as pressure, heat, or the transitory sting or itch caused by an *applied skin care product*." See Hahn at Col. 8, ll. 55-60 (emphases added). Here again, Hahn provides evidence supporting Appellant's assertion that teachings to reduce superficial skin irritations are not combinable with those directed to reducing internal causes, i.e., disease states associated with resultant inflammation. Therefore, Appellant submits that this passage in Hahn, alone, would be sufficient to deter one skilled in the art from even trying any agent other than an anti-irritant, such as the anti-inflammatory compounds of Williamson and Wahl. Appellants Brief dated July 30, 2003, page 9, lines 1-8.

Illustrated graphically below, it becomes clear that the teachings of Hahn, when compared with those of Williamson and Wahl, seek different treatments points. As such, the combination relied upon by the Examiner is unsupported in the art.



B. Williamson and Wahl

Attempting to refute Appellant's arguments, the Examiner states that: (1) "Wahl teaches inhibiting the nitric oxide at the site of inflammation"; (2) "all the references are directed to skin inflammatory conditions (dermatitis, psoriasis) caused by chemical or physical agents and Williamson and Wahl suggest that the inflammation in dermatitis or psoriasis, respectively, involves the increased production of nitric oxide"; (3) "Wahl suggests topical application of NO synthase inhibitors"; and (4) "Hahn and Williamson teach the treatment of skin conditions such as dermatitis caused by skin irritants."

Examiner's Answer at page 6, lines 17-18; page 7, lines 3-6, line 11, lines 16-17.

Addressing each of these remarks in turn, Appellant continues to maintain that the

absence of any teaching or suggestion in Hahn of systematically combating *inflammation* and the absence of any teaching or suggestion in Williamson and Wahl of combating symptomatic *irritation* have been ignored by the Examiner because the word "dermatitis" and/or "psoriasis" appears in the references. Appellant submits that the relied upon references warrant further consideration by the Examiner.

The Examiner asserts: (1) Wahl teaches inhibiting the nitric oxide at the site of inflammation, and (3) Wahl suggests topical application of NO synthase inhibitors.

The Examiner's statements that "Wahl teaches inhibiting the nitric oxide at the site of inflammation" and "Wahl suggests topical application of NO synthase inhibitors" are not contended by Appellant. Appellant, however, strongly disputes that these statements supply some sort of motivation for the combination of Wahl's teachings with those of Hahn.

Wahl's disclosure provides a means to interfere with the production of nitric oxide ("NO") by leukocytes activated by bacteria, bacterial products, T lymphocyte-derived cytokines, and antigens. See generally, Wahl at Col. 1, ll. 24-59. Wahl teaches that "the compounds of the present invention . . . may be delivered or administered topically, by transdermal patches, intravenously, locally, intra-articularly . . . [i]ntravenous administration is preferred." Wahl at Col. 6, ll. 54-59. Although Wahl suggests the topical administration of certain compounds to combat NO production, this teaching does not change that Wahl treats the source of the problem. The source of the problem being the systemic production of NO by leukocytes activated by bacteria, bacterial products, T lymphocyte-derived cytokines, and antigens. See Wahl at Col. 6, ll. 54-59.

Wahl unquestionably does not suggest treating the symptoms that signal NO production.

The compounds taught in Wahl, NO synthase inhibitors, are not taught or even suggested as non-systemic anti-irritants. Therefore, the only logical way that the Examiner could have come to this conclusion is through hindsight vision using the lens of Appellant's specification, which teaches NO synthase inhibitors as anti-irritants. Specification at page 3, lines 16-18; see also, Appellant's Brief dated July 30, 2003, pages 14-15, for a detailed discussion and identification of legal support prohibiting the use of hindsight reconstruction.

The Examiner asserts: (2) All the references are directed to skin inflammatory conditions (dermatitis, psoriasis) caused by chemical or physical agents and (4) Hahn and Williamson teach the treatment of skin conditions such as dermatitis caused by skin irritants.

The Examiner attempts to combine the cited references by alleging "all the references are directed to skin inflammatory conditions (dermatitis, psoriasis) caused by chemical or physical agents . . ." Examiner's Answer at page 7, lines 3-6. Similarly, the Examiner contends that "Hahn and Williamson teach the treatment of skin conditions such as dermatitis caused by skin irritants." *Id.* at page 7, lines 16-17. Although each reference does recite the term "dermatitis," Hahn treats the skin symptom of irritation associated with dermatitis, while Williamson and Wahl treat the systemic skin condition of dermatitis/inflammation itself. Appellant's Brief dated July 30, 2003, at page 10, lines 3-13.

For example, to reach the conclusion that all the references treat the same condition, the Examiner reads out of context the disclosure of Hahn concerning conditions such as psoriasis and contact dermatitis. Examiner's Answer at page 3, lines 11-17. Hahn's disclosure cited by the Examiner discusses psoriasis and contact dermatitis only as a condition that makes the skin more vulnerable to topically applied skin irritants, such as chemicals. Hahn at Col. 3, ll. 28-43. Specifically, Hahn states that psoriasis and contact dermatitis "produce *intrinsic* irritation which may be exacerbated by application of topical products." Hahn at Col. 3, ll. 36-41 (emphasis added). There is an additional mention of skin diseases generally at Col. 10, ll. 12-19 where Hahn states that the invention is also "useful for preventing, reducing or eliminating the skin irritation caused by skin diseases," including "*intrinsic* irritation." Here again, Hahn's invention is directed toward relieving symptomatic irritation not the systemic problem. Therefore, regardless of the fact that the reference recites the word psoriasis or dermatitis, Hahn only discloses treatment of the symptom, i.e., irritation, not the treatment of the systematic problem, i.e., inflammation.

Furthermore, the Examiner continues to ignore the distinction between irritation and inflammation as evidenced by repeated assertions that "Hahn and Williamson teach the treatment of skin conditions such as dermatitis caused by skin irritants." See Examiner's Answer at page 7, line 16-17; see also page 5, line 21-page 6, line 3. As previously indicated, Hahn provides that divalent strontium is effective "to suppress the relatively severe stinging, burning, tingling itching and/or erythema induced by topical application . . . as well as the skin *irritants* glycolic acid, capsaicin, capryloyl salicylic

acid, benzoyl peroxide, and post-shaving-applied seawater." Hahn at Col. 11, II. 27-33 (emphasis added). Hahn is clearly directed to preventing and/or reducing skin *irritation.*¹

Irritation, as defined by Dorland's Illustrated Medical Dictionary 68 (26th ed. 1981), is defined functionally as "a state of over excitation and undue sensitivity; irritation due to direct stimulation of a part." In contrast, both Williamson and Wahl are directed to the prevention and/or reduction of nitric oxide production associated with inflammatory diseases. See generally, Williamson at Col. 2, II. 44-47; Wahl at Col. 2, II. 8-12.

Williamson is specifically directed to "administration of methyl-, dimethyl-, or amino-substituted guanidines as inhibitors of nitric oxide production in a host afflicted with acute or chronic inflammatory disease." Williamson at Col. 1, II. 24-27. Similarly, Wahl is directed to treating "an inflammatory condition, especially chronic, wherein an effective amount of an agent, which is capable of decreasing the amount of nitric oxide present, is administered." Wahl at Col. 2, II. 7-12. In both instances, Williamson and Wahl seek to inhibit NO production of inflammatory diseases.

Simply put, Williamson and Wahl are concerned with the treatment of the systemic condition itself, i.e., preventing inflammation (dermatitis), whereas Hahn is directed to the symptom of irritation caused by or associated with such a condition. Since none of the references characterizes inflammation as a degree of irritation nor

¹ In Hahn's twenty-five figures not one charts a measure of inflammation; instead, all figures chart irritation as do all of Hahn's examples. Hahn at Col. 17, line 1-Col. 22, line 27.

vice versa, it is improper for the Examiner to allege the terms dermatitis and inflammation are synonymous with irritation. Thus, Appellant respectfully submits that, in contrast to the unsupported assertions of the Examiner, Hahn fairly suggests that treating irritation associated with dermatitis is distinctly different from treating inflammation, as provided in Williamson and Wahl.

II. Conclusion

For the reasons of record and the reasons set forth above, Appellant maintains that a prima facie case of obviousness has not been established by the Examiner based on the cited references, either alone or in combination. The Examiner fails to demonstrate that one of ordinary skill in the art would have been motivated to make the Examiner's proposed modifications. Further, the Examiner fails to set forth any reason why one of ordinary skill in the art, even if such motivation exists, would have a reasonable expectation of success. Appellant maintains this position with respect to all issues covered by the Appeal Brief filed on July 30, 2003.

Accordingly, Appellant respectfully requests reversal of the rejection of claims 31-38, 40-54, and 56-66 under 35 U.S.C. § 103(a).

To the extent any further extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Reply Brief, such extension is hereby requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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GARRETT & DUNNER, L.L.P.

Dated: July 6, 2004

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Attachment: Excerpt from Dorland's Illustrated Medical Dictionary (26th ed. 1981).